Claim 36 (Previously presented) The polypeptide of claim 19 having an amino acid sequence further comprising an amino acid sequence having at least 95% identity to the amino acid sequence of the thrombospondin domain of SEQ ID NO: 2.

Claim 37 (Previously presented) The polypeptide of claim 19 having an amino acid sequence further comprising an amino acid sequence having at least 97% identity to the amino acid sequence of the thrombospondin domain of SEQ ID NO: 2.

Claim 38 (Previously presented) The polypeptide of claim 19 having an amino acid sequence further comprising an amino acid sequence having at least 99% identity to the amino acid sequence of the thrombospondin domain of SEQ ID NO: 2.

Claim 39 (Previously presented) The polypeptide of claim 19 having an amino acid sequence further comprising an amino acid sequence of the thrombospondin domain of SEQ ID NO: 2.

REMARKS

Claims 14 and 19-39 are pending in the subject application. Applicants have hereinabove amended claims 19-23 and 30-34. Accordingly, upon entry of this amendment claims 14 and 19-39 will be pending. Applicants respectfully request reconsideration of the subject application in view of the following remarks.

STATUS OF THE CLAIMS

Following entry of this Amendment, claims 14 and 19-39 will be pending. Claims 19-23 and 30-34 have been amended.

Support for the amended claims is as follows:

Claims 19-23: page 3, lines 28-32; and page 8, line 19.

Claims 30-34: page 3, lines 28-32; and page 8, line 19.

INFORMALITIES

Applicants acknowledge the Examiner's objection to the disclosure because it contains an embedded hyperlink at page 1, line 13. Applicants herein submit a replacement paragraph marked up to show changes made relative to the immediate prior version. An accompanying clean version is not required.

REJECTION UNDER 35 U.S.C. §101

Claims 14 and 19-39 stand rejected under 35 U.S.C. §101 on the basis that the claimed invention lacks patentable utility. Reconsideration of the rejection is respectfully requested in view of the arguments below.

The Examiner states that "while the human ADAMTS-E amino acid sequence of the SEQ ID NO: 2 herein shares a significant degree of sequence similarity with other members of the family of mammalian ADAMTS metalloproteases, nothing in the record shows that all, or a majority, of the members of the ADAMTS family-or the larger ADAM family-share a common activity with a common substrate." Further the Examiner states that "the record shows that only a single ADAMTS metalloprotease functions as an aggracanse, and the 31%-59% identity in the metalloprotease domain [of the ADAMTS-E] ... compared to other ADAMTS family member[s] that Applicant points to is insufficient to support any specific utility for the human ADAMTS-E having the amino acid sequence of SEQ ID NO: 2 herein."

Applicants' invention as recited in Claims 14 and 19-39 is drawn to a purified polypeptide having an amino acid sequence comprising an amino acid sequence having at least 90% identity to the amino acid sequence of the metalloproteinase domain of SEQ ID NO: 2, an amino acid sequence having at least 90% identity to the amino acid sequence of the disintegrin domain of SEQ ID NO 2, an amino acid sequence having at least 90% identity to the amino acid sequence of the prodomain domain of SEQ ID NO 2, and an amino acid sequence having at least

90% identity to the amino acid sequence of the thrombospondin domain of SEQ ID NO 2. The invention is also drawn to a method for identifying compounds, which inhibit, stimulate, or bind to this polypeptide.

Applicants wish to remind the Examiner that to be considered appropriate by the USPTO, any rejection based on lack of utility must include a detailed explanation why the claimed invention has no specific, substantial and credible utility, support for factual findings relied upon in reaching this conclusion, and specific evidence that supports any fact-based assertion needed to establish the *prima facie* showing. This the Examiner did not do. Although, the Examiner agrees with the Applicants that the polypeptide of the present invention shares a "significant" degree of sequence similarity with other members of the ADAMTS metalloproteases he states that "nothing in the record shows that all, or a majority of the members of the ADAMTS family-or the large ADAM family-share a common activity with a common substrate." Applicants remind the Examiner that an invention has a well-established utility, if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties of a product or obvious application of a process).

Applicants once again refer the Examiner to the Revised USPTO Utility Examination Guidelines regarding imputed utility.[1] The Guidelines state that "when a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein." The polypeptide of the present invention is a member of the family of proteins known as ADAMTS proteins. ADAMTS proteins exhibit characteristics of the well-characterized ADAM family of metalloproteases. Members of this family of proteins have the ability to degrade aggrecan, a high molecular weight proteoglycan which provides cartilage with important mechanical properties and which is lost during the development of arthritis. Applicants respectfully refer the Examiner to Figure 4 illustrating the metalloproteinase domain alignment of ADAMTS-E to other members of the

[1] Department of Commerce, USPTO Utility Examination Guidelines, December 29, 2000.

ADAMTS family as support for imputing utility to the protein of the present invention based on activity of members of the ADAMTS family. Applicants further refer the Examiner to page 1, lines 17-37 and page 2 lines 1-21 for a disclosure of other ADAMTS activities such as brevicanase activity and antiangiogenic activity which have been identified as having important roles in human disease. Applicants further refer the Examiner to page 21, lines 17-33 for a detailed disclosure of well-known assays for identifying activities of the polypeptide of the present invention. Applicants assert that a person of skill in the art would find readily apparent these activities and would be able without undue experimentation to assay for these activities using techniques known in the art.

Applicants further wish to remind the Examiner that a rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record. In the Federal Register, Vol. 64, No. 244 it states that "office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement... only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained."

Applicants argue that in general, a single accepted utility is sufficient to justify claims to a biological compound so that demonstrating a particular use for such a compound will suffice to meet the utility requirement. In Cross v. Iizuka, 753 F.2d 1040 (Fed. Cir. 1985) the Court found utility for a therapeutic invention even when Applicants were at a very early stage in the development of the pharmaceutical product. The polypeptide ADAMTS-E of the present invention was found to be present in heart, spleen, kidney, liver, brain and lung tissues (see Example 2, page 26, line 3). ADAMTS-E was also found to be expressed in chondrocytes isolated from osteoarthritic cartilage tissue (6 of 7 patients analyzed) (see Example 2, page 26, lines 5-6). As disclosed in Applicants' specification, page 2, lines 5-21, ADAMTS proteins and

ADAMTS protein stimulators and inhibitors have important therapeutic uses, including treatment of arthritis, organ transplant toxicity, osteoporosis, spinal cord injury, migraine, congestive heart failure, stroke, neurodegenerative diseases, multiple sclerosis and other diseases characterized by metalloproteinase activity. Applicants argue that event if the entire realm of substrates for the enzymatic activity of the polypeptide is not known, the substrates and role of the purified ADAMTS-E protein can be easily tested using techniques known to those skilled in the art. See, e.g., P.D. Brown et al., *Independent expression and cellular processing of Mr 72,000 type IV collagenase and interstitial collagenase in human tumorigenic cell lines*, 50(19) Cancer Research 6184 (October 1990); F. Vazquez et al., *METH-1 a human ortholog of ADAMTS-1, and METH-2 are members of a new family of proteins with angio-inhibitory activity*, 274 The Journal of Biological Chemistry 23349 (Aug. 1999); E.C. Arner et al., *Generation and characterization of aggrecanase*, 274 The Journal of Biological Chemistry 6594 (Mar. 1999); A. Colige et al., *cDNA cloning and expression of bovine procollagen I N-proteinase: A new member of the superfamily of zinc-metalloproteinases with binding sites for cell and other matrix components* 94 Proceedings of the National Academy of Sciences (USA) 2374 (March 1997).

Further, substrates for the polypeptide of the invention may be identified by a candidate protein or synthetic substrate approach. For example, candidate proteins can be cast within an agarose gel matrix and the ability of the ADAMTS-E protein to digest the protein determined using protein zymography. See, P.D. Brown et al., *Independent expression and cellular processing of Mr 72,000 type IV collagenase and interstitial collagenase in human tumorigenic cell lines*, 50(19) Cancer Research 6184 (October 1990). Alternatively, a phage display or fluorometric peptide library can be screened to identify substrates of the protein. See, D.R. O'Boyle et al., *Identification of a novel peptide substrate of HSV-1 protease using substrate phage display*, 236(2) Virology 338 (September 1997).

Applicants respectfully submit that the U.S. Patent and Trademark Office has no statutory authority, nor any judicially created authority, to require Applicants to show absolute proof of biological activity. Nor does the PTO have any authority to question the Applicants'

disclosed specific activity. As stated in the USPTO Utility Examination Guidelines "if the applicant has asserted that the claimed invention is useful for any particular purpose (i.e., "a specific utility") and that assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." Further, the Guidelines state that "credibility is to be assessed from the perspective of one of ordinary skill in the art in view of any evidence of record (e. g. data, statements, opinions, references, etc.) that is relevant to the applicant's assertions." The Guidelines further state that an Examiner "must accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion... when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner... . A rigorous correlation need not be shown in order to establish practical utility; reasonable correlation is sufficient."[2] The polypeptide of the present invention shares 31-59% identity in the metalloprotease domain as compared to other ADAMTS family members further supporting Applicant's statement of utility.

Most importantly, the Guidelines state that "an applicant must provide only one credible assertion of specific utility for any claimed invention to satisfy the utility requirement. It is Applicants' right under 35 U.S.C. § 101 to state the specific utility for the claimed invention as they see it and this the Applicants have done.

The claims as now presented are drawn to an isolated polypeptide and Applicants assert the claimed invention has a practical and well-known utility. In view of these arguments, Applicants request that the rejection of claims 14 and 19-39 under 35 U.S.C. §101 be withdrawn.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 14 and 19-39 are rejected under 35 U.S.C. §112, first paragraph because the specification does not enable any person skilled in the art to use the invention commensurate in

[2] Fujikawa v. Wattanasin, 93 F.3d 1559, 1565 (Fed. Cir. 1996).

scope with the claims. The primary basis for the rejection appears to be that since the disclosed amino acid sequence of SEQ ID NO: 2, described by claim 24 is not supported by either a specific asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention.

In view of the arguments presented above with respect to utility, Applicants respectfully assert that this is no longer a valid rejection and request withdrawal of the rejection of claims 14 and 19-39 under 35 U.S.C. §112, first paragraph for lack of enablement.

Claims 14, 19-23, and 25-39 are rejected under 35 U.S.C. §112, first paragraph as containing matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner states that the specification fails to exemplify or describe the preparation of the subject matter of divergent ADAMTS-E polypeptides of claims 14, 19-23 and 25-39 or a method of use of the divergent ADAMTS-E polypeptides of claim 19.

In response, Applicants refer the Examiner to page 13, lines 34-37, page 14, lines 1-37, page 15, lines 1-14, and page 17, lines 29-37 for a description of the various ways to express and isolate the polypeptide of the present invention. Further, Applicants refer the Examiner to Example 1, page 25, lines 5-31 for a detailed description of the identification of the polypeptide of the present invention as claimed in claims 14, 19-23, and 25-39.

In view of Applicants' assertion that a person of skill in the art would find readily apparent the identification, expression, and isolation of the polypeptide of the present invention and Applicants argument that a person skilled in the art would be able without undue experimentation to perform these assays using techniques known in the art the rejection is no longer valid. Applicants respectfully assert that this is no longer a valid rejection and request withdrawal of the rejection of claims 14, 19-23, and 25-39 under 35 U.S.C. §112, first paragraph.

The Examiner has further rejected claims 14, 19-23, and 25-39 because "the specification is not enabling for embodiments of a metalloprotease having an amino acid sequence wherein a

metalloprotease domain diverges from the amino acid sequence of SEQ ID NO: 2 by amino acid substitutions, deletions and insertions, or combinations thereof at as many as 38 amino acid positions, or even 4 amino acid positions, within SEQ ID NO: 2."

In response to this rejection, claims 19-23 have been amended in a manner which, Applicants believe address the basis of the Examiner's rejection. Specifically, the amended claims encompass a narrow scope of subject mater. Amended claims 19-23 incorporate the limitations of claims 24-29 and 35-39. One skilled in the art would, it is submitted, readily be able to synthesize and use the polypeptide as claimed within the relatively narrow range encompassed. Applicants further argue that the scope of claims as amended is such, it is submitted, that the functional characteristics of the invention are supported by Applicants' disclosure of the sequences shown, and activities of the particular domains described. Therefore, withdrawal of the rejection on this basis is respectfully requested. Applicants assert that the claims as now presented are sufficiently enabling to allow one of skill in the art to make and use the invention as claimed without undue experimentation.

In view of the amendment to the claims, and comments above, withdrawal of the rejection of claims 14, 19-23, and 25-39 under 35 U.S.C. §112, first paragraph for lack of enablement is respectfully requested.

REJECTION S UNDER 35 U.S.C. §102(e)

Claims 14, 19-23, and 30-34 stand rejected under 35 U.S.C. §102(e) as anticipated by Heller et al., published U.S. patent Application No. 2002/0107361 (hereinafter "Heller"). This rejection is based on the disclosure of the amino acid sequence of the MPTS-10 human metalloprotease.

In response to this rejection, Applicants have amended claims 19-23 and 30-34 to incorporate the limitations of claims 24-29 and 35-39. As the Examiner states in his September 9, 2003 Office Action, "Heller et al is not prior art to the new claims 24-29 and 35-39."

Withdrawal of the rejection of claims 14, 19-23, and 30-34 as anticipated by Heller et al. is respectfully requested.

In view of the amendment to claims 19-23 and 30-34, and Applicants arguments regarding utility, withdrawal of the rejection of claims 14, 19-23, and 30-34 under 35 U.S.C. §102 for lack of novelty is respectfully requested.

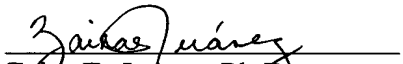
CONCLUSION

For the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the grounds for rejection set forth in the September 9, 2003 Office Action. In view of the foregoing amendments and remarks, Applicants respectfully submit that the instant application is now in condition for allowance. Issuance of a notice to that effect is respectfully solicited.

If the Examiner wishes to comment or discuss any aspect of this application or response, Applicants' undersigned attorney invites the Examiner to call her at the telephone number provided below.

Respectfully submitted,

Dated: Jan. 13, 2004



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